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(54) PULSATILE PARTICLES DRUG DELIVERY SYSTEM

ARZNEIABGABESYSTEM MIT STOSSWEISER FREISETZUNG VON PARTIKELN

SYSTEME D'ADMINISTRATION PULSATIL DE MEDICAMENTS SOUS FORME DE PARTICULES

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Description

Technical Field

[0001] My invention relates to controlled absorbtion drug delivery systems and more particularly to combined coating dissolution and explosion mechanisms in coated drug-containing pellets for assured timely release of orally administered pharmaceuticals.

Background Art

[0002] A unique sustained-release drug delivery system, Time-Controlled Explosion System (TCES), was described in U. S. Patent 4,871,549 issued 10/3/89 to Ueda et al. Drug release is caused by explosion of an insoluble, water permeable membrane after a definite period of time. Beads or granules contain the drug and a swelling agent enclosed by the water insoluble membrane. Water permeates the membrane and causes the swelling agent to expand until the internal forces on the membrane cause it to burst or explode, thereby releasing the drug. This mechanism is especially useful with water insoluble drugs in which those prior art delay mechanisms related to diffusion of the drug through a permeable coating would not be effective.

[0003] A remarkable feature of the TCES is that drug is not released from the completely coated pellets or spheres until the membrane bursts, and then it is all available. This can provide for a pulse of drug release. The lag time before release is related to the thickness of the membrane with maximum lag times of approximately four hours reported by Ueda.

[0004] One of the principal uses for delayed release forms of medication is to provide for a once a day oral administration that releases drug in a continuous controlled rate or in a series of sequential pulses throughout the 24 hour period. This ensures a reasonably uniform blood level for maximum efficacy with the least toxic effect from high peaks of blood concentration. This is not easily accomplished with the system of Ueda because the insoluble membrane must be made very thick for long delays, and this makes explosion less reliable. If the membrane never bursts, the drug will be lost in the stool and the patient will get less drug than prescribed and never be aware of it. Furthermore, in cases where there is a delayed stomach emptying time, much of the explosion may take place in the stomach and not be available for absorbtion until the pyloric sphincter opens. This may present a very large dose for sudden absorbtion that may be very dangerous. Furthermore, acid unstable drugs should not be released to the acidic stomach contents, where an indeterminate portion of the drug dose may be destroyed.

[0005] US 3,247,066 describes a controlled release dosage form for administering a drug, consisting of a core surrounded by a film coating. The core comprising a water-swellable colloid material containing the drug, and the film coating is a water insoluble polymer.

[0006] US 3,247,066 further discloses (column 1, lines 60-65) that the leaching mechanism can be obtained by coating the drug with a film comprising a water soluble polymer which allows the drug diffusing through the pores.

Disclosure of the Invention

[0007] It is accordingly an object of the invention to provide unit dosage forms for drugs or therapeutic agents that will release the drug into the environment of use in a series of sequential, pulsatile releasing events that employs conventional pharmaceutical equipment and products such as roller compaction methods for optimum economy, reliability and bioavailability. It is another object to provide dosage units readily adaptable to a variety of timing intervals, different therapeutic agents and combinations of agents, including agents which cannot be released by diffusion through an insoluble coating. It is yet another object to provide a system that can yield a large number of pulses within a single unit dosage form at no significant increase in cost over only one or two pulses. It is yet another object of the invention to provide means for protecting the drug from adverse environmental conditions prior to delivery into the environment of use. It is yet another object of the invention to provide a drug delivery system in which the explosive pellets mechanism for drug release is modified by changing the coating to delay the explosion event in a more controllable and reliable fashion than simply increasing the thickness of the insoluble coating.

[0008] The coating of the invention is provided with two means to alter release time of the drug. A first means for altering of the invention comprises the incorporation of a water soluble polymer along with the insoluble, water permeable coating material of the prior art. This water soluble polymer is of the enteric coating polymer type in which the polymer becomes soluble only at pH values above certain specific values. This prevents dissolving of the polymer in the stomach. When the pellet reaches the elevated pE of the intestine, the polymer begins to dissolve and weaken the membrane coating, so that explosion of the weakened membrane can be assured after a predetermined time of exposure to the intestinal environment. By varying the proportion of soluble and insoluble material in the coating as well as the coating thickness, the time delay before explosion can be prolonged with better control and reliability, with

eventual disintegration of the coating ensuring release of the drug.

[0009] A second means for altering release of the drug comprises the incorporation into the coating of material which reduces the permeability of the coating. By reducing the rate of influx of water into the interior of the pellet containing the swelling agent, the rate of swelling can be reduced and the time to explosion can be prolonged and controlled. Either of these means of modifying the coating may be used separately or in combination.

[0010] These and other objects, advantages and features of the invention will become more apparent when the detailed description is studied in conjunction with the drawings.

Brief Description of the Drawings

[0011]

Fig. 1 shows diagrammatically a pellet of the invention with a core prepared by roller compaction with a mixture of swelling agent and active drug.

Fig. 2 shows diagrammatically a pellet of the invention with a core of a sugar seed coated with a mixture of swelling agent and active drug.

Fig. 3 shows diagrammatically a unit dose of the invention with pellets having five different release times.

Best Mode for Carrying Out the Invention

[0012] Referring now first to Fig. 1, an individual pellet 2 of the invention comprises a core 1 prepared by the well known, economical, roller compaction method with sieving to select granules of particular mesh size and irregular configuration containing a combination of active drug 3 and swelling agent 4. The coating membrane 5 completely encloses the core 1. The coating membrane contains:

a) a water insoluble, water permeable polymer;
b) an enteric coating polymer (a polymer soluble in water values above a certain value;
c) a diffusion controlling agent which reduces the permeability of the coating to water.

[0013] Referring now to Fig. 2, an individual pellet 6 of the invention comprises a bead core 7 of sugar. This is coated with a layer of a mixture of active drug 3 and swelling agent 4 by spray coating in a fluidized bed as is well known in the art. The layer of active drug and swelling agent is then enclosed by an outer coating membrane 5. The coating membrane contains:

a) a water insoluble, water permeable polymer;
and one or both of:
c) a diffusion controlling agent
d) a dissolution controlling agent

[0014] The preparation and coating of the pellets may be performed by any of the processes well known in the art, and the order in which the various ingredients are laid down may be varied as desired, with drug and swelling agent inside the frangible coating. The frangible coating may be constructed to increase or decrease the lag time to release by varying the proportions of insoluble polymer, soluble polymer and diffusion controlling agent. The thickness of the outer coating and the amount of swelling agent may also be adjusted. When control must be exerted over where in the digestive tract release is to occur, the dissolution agent may be of the enteric type wherein solubility increases at higher pH.

[0015] The system may be used with water soluble as well as water insoluble drugs or combinations of drugs.

[0016] Water permeable and insoluble film-forming polymer materials for the coating may include cellulose derivatives, acrylic resins, copolymers of acrylic acid and methacrylic acid esters with quaternary ammonium groups and copolymers of acrylic acid and methacrylic acid esters. Permeation retarding materials may include ingredients such as the fatty acids, waxes, and the salts of the fatty acids such as magnesium stearate and calcium stearate. The pharmaceutical grades may not be pure stearates, but may contain small amounts of other fatty acid salts.

[0017] Swelling agents may include:

cross-linked polyvinyl pyrrolidone
cross-linked carboxymethylcellulose;
sodium starch glycolate and pregelatinized starch.

[0018] Water permeable and soluble film forming agents may include the enteric polymers which have greatly increased solubility at alkaline pH such as: cellulose acetate phthalate; cellulose acetate trimellitate; shellec; methacrylic acid copolymers, USP/NF, such as the Eudraget formulations of Rohm Pharma GMBH of Weiterstadt; and hydroxypropyl methylcellulose phthalate.

[0019] Water permeable and slowly soluble film forming agents whose solubility is substantially independent of pH include hydroxypropyl methylcellulose and polyvinyl pyrrolidone.

[0020] According to an embodiment of the unit dosage form of the invention, said water-insoluble film forming polymer comprises no less than half of the membrane

[0021] The following examples describe typical formulations of multiparticulate, pulsatile unit dosage forms and methods of manufacture thereof:

Example 1

[0022]

Nifedipine, a drug	200 g
Explotab, a swelling agent, a starch glycolate	200 g
Povidone K90, a binding agent, polyvinyl pyrrolidone	20 g
Ethanol	1800 g

[0023] The above three raw materials were first dispersed in the ethanol until uniform. The suspension was then spray coated onto 400 g of sugar spheres (size 40 to 50 mesh) in a fluidized bed coater equipped with a Wurster column. Six hundred grams of the Nifedipine pellets are then coated with the following polymer suspension:

Ethylcellulose, an insoluble polymer	90 g
Eudragit SI00, an ethacrylic acid copolymer slowly soluble in intestinal fluid	45 g
Magnesium Stearate, a hydrophobic agent reducing permeability	15 g
Ethanol	1800 g

[0024] At the time intervals when about 25%, 50% and 75% of the coatings suspension are consumed, the coating machine is stopped and 50 grams of samples are collected. Then coating continues until all of the coating material is consumed. These four samples coated with different amounts of polymer will give various lag times when placed in an aqueous medium.

Forty grams of the above four types (i.e. coated with four different levels of polymer) of coated pellets are then mixed with 25 grams of microcrystalline cellulose, 13 grams of Polyplasdone XL, a cross-linked PVP disintegrant from GAF Chemical Corp., and 2 grams of Myvatex, a lubricant for compression. The above mixture is then compressed into suitable size of tablets. This tablet will give a pulsatile pellet delivery system with four different releasing lag times. The four types of coated pellets can also be blended and encapsulated in a capsule dosage form.

Example 2

[0025]

Zidovudine, a drug	200 g
Explotab	200 g
Povidone K O	20 g
Ethanol	1800 g

[0026] The above three raw materials were first dispersed in the ethanol until uniform. The suspension was then spray coated onto 400 g of sugar spheres (size 40 to 50 mesh) in a fluidized bed coater equipped with a Wurster column. Six hundred grams of the zidovudine pellets are then coated with the following polymer suspension:

Ethylcellulose	90 g
HPMCP 55, enteric polymer, hydroxypropyl methylcellulose phthalate, Eastman	45 g
Magnesium Stearate	15 g

(continued)

Ethanol	1800 g

[0027] At the time interval when about 50% of the coatings suspension are consumed, the coating machine is stopped and 50 grams of samples are collected. Then coating is resumed until all of the coating material is consumed. These two samples coated with different amounts of polymer will give different lag times when placed in an aqueous medium.

Forty five grams of the above two types (i.e. coated with two different levels of polymer) of coated pellets are then mixed with 45 grams of uncoated active pellets (for immediate release purpose), 7 grams of microcrystalline cellulose, 6 grams of Polyplasdone XL and 2 grams of Myvatex. The above mixture is then compressed into suitable size of tablets. This tablet will give a pulsatile pellet delivery system with three different releasing lag times.

[0028] The combination of a water soluble film forming agent with a permeability reducing agent in the coating with the insoluble film forming agent gives greater control over the frangibility of the coating and the rate of swelling.

[0029] Fluidized bed coaters are well known in the art and have been found useful in this process but other coating apparatus and methods well known in the art may be used with the invention as well.

[0030] The term "drug" as used herein includes, without limitation, antibiotics, tranquilizers, agents acting on the heart, liver, kidney, central nervous system and muscles, contraceptives, hormonal agents, antineoplastic agents useful in humans or animals and may include combinations of drugs.

[0031] The term "unit dosage form" includes, without limitation, discrete aggregates of populations of pellets contained in capsules, or compressed into tablets or suppositories with binding agent. The dosage form may be arranged to dissolve promptly in any aqueous medium or to resist dissolution in certain environments such as enteric coated tablets which will not release pellets until they have passed the acid stomach and reached the alkaline intestine.

[0032] Referring now to Fig. 3, a typical unit dosage form is shown diagrammatically as a carrier medium such as a tablet or a capsule 8 holding five populations of pellets. All of the pellets have identical cores containing swelling agent 4 and drug 3. All of the pellets have a coating that includes a water permeable and insoluble film forming agent. The coatings of the different populations are provided with other ingredients as well, to alter the time interval between initial exposure to water and final bursting of the pellet from imbibition of water and swelling.

[0033] The first-to-burst population of pellets 10 are provided with a high concentration of water soluble film forming agent indicated by circles 11. As the agent 11 is rapidly removed from the coating, the coating becomes more frangible, and is burst by a lower internal pressure from the swelling agent. The second-to-burst population of pellets 12 have a lower concentration of soluble film forming agent 11 which extends the time before the coating becomes so weak from loss of the agent that it bursts. The third-to-burst population of pellets 13 has, in addition to the water soluble film forming agent 11, some hydrophobic or permeability reducing agent 14 in the coating to slow down the rate at which water enters the core to swell the swelling agent 4. This increases the time lag before the pellets burst, releasing their contents. A fourth-to-burst population of pellets 15 has a coating with only permeability reducing agent 14 added in small concentration to reduce the rate of swelling. The fifth-to-burst population of pellets 16 is provided with a higher concentration of hydrophobic agent 14 to further reduce the rate of swelling to prolong further the lag time before release of the drug 3 for absorbtion.

[0034] The particles or pellets of the invention may include without limitation spheres, irregular shapes or large tablet shapes such as the well known "minitablets", for example, and their sizes may vary between 4 mm. down to about 0.1 mm.

[0035] The above disclosed invention has a number of particular features which should preferably be employed in combination although each is useful separately without departure from the scope of the invention. While I have shown and described the preferred embodiments of my invention, it will be understood that the invention may be embodied otherwise than as herein specifically illustrated or described, and that certain changes in the form and arrangement of parts and the specific manner of practicing the invention may be made within the underlying idea or principles of the invention within the scope of the appended claims.

Claims

1. A unit dosage form for releasing a drug into an aqueous-fluid-containing environment in a plurality of sequential, pulsatile releasing events, said unit dosage form comprising:

   A) a capsule or tablet which disintegrates in an aqueous environment of use;
   B) a plurality of populations of pellets or particles enclosed within said capsule or tablet, each population of pellets constructed to release a drug into said environment of use by bursting at a different particular release

time interval after initial contact with said environment of use, whereby all of said pellets are released from said capsule or tablet substantially simultaneously and exposed to said environment of use substantially simultaneously when said capsule or tablet disintegrates;

C) each pellet containing a core including said drug and a swelling agent other than said drug, said swelling agent having the property of increasing in volume on exposure to water; and

D) a frangible, water-permeable membrane completely enclosing said core and preventing release of said drug into said environment of use, said membrane comprising at least one water-insoluble film forming polymer and at least one of:

a) a water-soluble film forming polymer means which gradually dissolves and causes said membrane to become increasingly frangible as time in contact with water increases; and

b) a permeability-reducing means which reduces the rate at which water passes through the membrane and thereby the rate of increase in volume of the swelling agent in the core, whereby the increasing volume of said swelling agent applies increasing internal force on said membrane and the rate at which said force is applied is determined by the water-permeability of said membrane, and the internal force at which said membrane will burst is determined by the frangibility of said membrane, and drug is released to said environment of use when the membrane enclosing said core bursts.

2. The unit dosage form according to claim 1, in which all of the populations have membranes with the same composition and the particular release time of a population is determined by the thickness of said membrane.

3. The unit dosage form according to claim 1, in which the particular release time of a population is determined at least in part by the relative proportions of said insoluble film forming polymer, said water-soluble film forming polymer means and said permeability reducing means in said membrane.

4. The unit dosage form according to claim 1, in which said water-soluble film forming polymer means has a greater solubility at alkaline pH.

5. The unit dosage form according to claim 1, in which said water-soluble film forming polymer means is substantially soluble at both alkaline, neutral and acid pH.

6. The unit dosage form according to claim 1, in which said swelling agent is selected from the group consisting of; cross-linked polyvinyl pyrrolidone; cross-linked carboxymethylcellulose; sodium starch glycolate and pregelatinized starch.

7. The unit dosage form according to claim 6, in which said water-insoluble film forming polymer is selected from the group consisting of: cellulose derivativess; acrylic resins; copolymers of acrylic acid and methacrylic acid esters with quaternary ammonium groups; and copolymers of acrylic acid and methacrylic acid esters.

8. The unit dosage form according to claim 7, in which said permeability-reducing means is selected from the group consisting of: fatty acids; waxes; and the salts of the fatty acids.

9. The unit dosage form according to claim 8, in which said water-soluble film forming polymer means is selected from the group consisting of: cellulose acetate phthalate; cellulose acetate trimellitate; hydroxypropyl methylcellulose phthalate; hydroxypropyl methylcellulose; polyvinyl pyrrolidone; shellac; and methacrylic acid copolymers.

10. The unit dosage form according to claim 1, in which said water-insoluble film forming polymer is selected from the group consisting of: cellulose derivatives; acrylic resins; copolymers of acrylic acid and methacrylic acid esters with quaternary ammonium groups; and copolymers of acrylic acid and methacrylic acid esters.

11. The unit dosage form according to claim 1, in which said permeability-reducing means is selected from the group consisting of: fatty acids; waxes; and the salts of the fatty acids.

12. The unit dosage form according to claim 1, in which said water-soluble film forming polymer means is selected from the group consisting of: cellulose acetate phthalate; cellulose acetate trimellitate; hydroxypropyl methylcellulose phthalate; hydroxypropyl methylcellulose; polyvinyl pyrrolidone; shellac; and methacrylic acid copolymers.

13. The unit dosage form according to claim 1, in which said water-insoluble film forming polymer comprises no less

than half of the membrane.

14. A method for preparing a unit dosage form for releasing a drug into an aqueous fluid environment in a series of sequential, pulsatile releasing events, the method comprising the steps of:

A) preparing a plurality of pellets or particles comprising a drug and a swelling agent other than said drug;
B) completely enclosing each pellet or particle within a water-permeable frangible coating or membrane, the membrane arranged to admit water to said swelling agent and to burst when said swelling agent has expanded and thereby applied a particular force on said membrane;
C) composing said coating from a mixture comprising: water-permeable insoluble film forming polymer, water-permeable soluble film forming polymer; and a permeability reducing agent;
D) dividing said pellets into a plurality of populations of pellets in which each population is provided with pellets having a coating arranged to cause said pellets to burst open and release the drug at a particular burst time interval after becoming exposed to said aqueous fluid environment, and providing each population with a coating having a different burst time interval to thereby provide said sequential, pulsatile releasing events;
E) mixing the plurality of populations of pellets in a predetermined proportion mixture; and
F) completely enclosing an aggregate of said mixture into a capsule or tablet which disintegrates in an aqueous fluid environment and releases said pellets to exposure to said aqueous fluid environment substantially simultaneously, to thereby prepare a unit dose in which said water-permeable soluble film forming polymer gradually dissolves and causes said coating to become increasingly frangible as time in contact with the aqueous fluid environment increases and said permeability reducing agent decreases the rate at which water passes through the membrane and thereby the expanding of said swelling agent, and the relative amounts of said soluble film forming polymer and said permeability reducing agent in coatings of each population, and the thickness of the coating, determine said particular burst time interval.

15. The method according to claim 14, in which the relative proportions of insoluble film forming polymer, soluble film forming polymer and permeability reducing agent are held constant in the coatings of all said populations and different burst time intervals are achieved by varying coating thickness.

16. The method according to claim 14, in which different burst time intervals are arranged by varying the relative proportions of said soluble film forming polymer, said insoluble film forming polymer, and said permeability reducing agent.

Patentansprüche

1. Dosierungseinheitsform zur Freisetzung eines Arzneistoffes in eine eine wäßrige Flüssigkeit enthaltende Umgebung in einer Mehrzahl von sequentiellen, stoßweisen Freisetzungsereignissen, wobei besagte Dosierungseinheitsform umfaßt:

A) eine Kapsel oder Tablette, die in einer wäßrigen Gebrauchsumgebung zerfällt;

B) eine Mehrzahl von Populationen von Pellets oder Teilchen, die in besagter Kapsel oder Tablette eingeschlossen sind, wobei jede Population von Pellets so konstruiert ist, daß sie durch Aufbrechen in einem unterschiedlichen bestimmten Freisetzungszeitintervall nach anfänglichem Kontakt mit besagter Gebrauchsumgebung einen Arzneistoff in besagte Gebrauchsumgebung freisetzt, wodurch alle besagten Pellets aus besagter Kapsel oder Tablette im wesentlichen gleichzeitig freigesetzt und besagter Gebrauchsumgebung im wesentlichen gleichzeitig ausgesetzt werden, wenn besagte Kapsel oder Tablette zerfällt;

C) wobei jedes Pellet einen Kern enthält, der besagten Arzneistoff und ein von besagtem Arzneistoff verschiedenes Quellungsmittel einschließt, wobei besagtes Quellungsmittel die Eigenschaft hat, bei Einwirkung von Wasser an Volumen zuzunehmen; und

D) wobei eine zerbrechliche, wasserdurchlässige Membran besagten Kern vollständig umschließt und die Freisetzung besagten Arzneistoffes in besagte Gebrauchsumgebung verhindert, wobei besagte Membran wenigstens ein wasserunlösliches filmbildendes Polymer und wenigstens eines von folgenden umfaßt:

a) ein wasserlösliches filmbildendes Polymermittel, das sich allmählich auflöst und bewirkt, daß besagte

Membran in zunehmendem Maße zerbrechlich wird, wenn die Kontaktzeit mit Wasser zunimmt; und

b) ein die Durchlässigkeit verringerndes Mittel, das die Geschwindigkeit verringert, mit der Wasser durch die Membran hindurchtritt, und dadurch die Geschwindigkeit der Zunahme des Volumens des Quellungsmittels im Kern, wodurch das zunehmende Volumen besagten Quellungsmittels zunehmende innere Kraft auf besagte Membran ausübt und die Geschwindigkeit, mit der besagte Kraft ausgeübt wird, durch die Wasserdurchlässigkeit besagter Membran bestimmt wird, und die innere Kraft, bei der besagte Membran brechen wird, durch die Zerbrechlichkeit besagter Membran bestimmt wird, und Arzneistoff in besagte Gebrauchsumgebung freigesetzt wird, wenn die Membran, die besagten Kern umschließt, bricht.

2. Dosierungseinheitsform nach Anspruch 1, **dadurch gekennzeichnet, daß** alle Populationen Membranen mit derselben Zusammensetzung besitzen und die bestimmte Freisetzungszeit einer Population durch die Dicke besagter Membran bestimmt wird.

3. Dosierungseinheitsform nach Anspruch 1, **dadurch gekennzeichnet, daß** die bestimmte Freisetzungszeit einer Population wenigstens teilweise durch die relativen Anteile besagten unlöslichen filmbildenden Polymers, besagten wasserlöslichen filmbildenden Polymermittels und besagten die Durchlässigkeit verringernden Mittels in besagter Membran bestimmt wird.

4. Dosierungseinheitsform nach Anspruch 1, **dadurch gekennzeichnet, daß** besagtes wasserlösliche filmbildende Polymermittel eine größere Löslichkeit bei alkalischem pH besitzt.

5. Dosierungseinheitsform nach Anspruch 1, **dadurch gekennzeichnet, daß** besagtes wasserlösliche filmbildende Polymermittel im wesentlichen bei sowohl alkalischem, neutralem als auch saurem pH löslich ist.

6. Dosierungseinheitsform nach Anspruch 1, **dadurch gekennzeichnet, daß** besagtes Quellungsmittel ausgewählt ist aus der Gruppe, die aus vernetztem Polyvinylpyrrolidon; vernetzter Carboxymethylcellulose; Natriumstärkeglykolat und vorgelatinierter Stärke besteht.

7. Dosierungseinheitsform nach Anspruch 6, **dadurch gekennzeichnet, daß** besagtes wasserunlösliche filmbildende Polymer ausgewählt ist aus der Gruppe, die aus Cellulosederivaten; Acrylharzen; Copolymeren von Acrylsäure- und Methacrylsäureestern mit quartären Ammoniumgruppen; und Copolymeren von Acrylsäure- und Methacrylsäureestern besteht.

8. Dosierungseinheitsform nach Anspruch 7, **dadurch gekennzeichnet, daß** besagtes die Durchlässigkeit verringernde Mittel ausgewählt ist aus der Gruppe, die aus Fettsäuren; Wachsen; und den Salzen der Fettsäuren besteht.

9. Dosierungseinheitsform nach Anspruch 8, **dadurch gekennzeichnet, daß** besagtes wasserlösliche filmbildende Polymermittel ausgewählt ist aus der Gruppe, die aus Celluloseacetatphthalat; Celluloseacetattrimellitat; Hydroxypropylmethylcellulosephthalat; Hydroxypropylmethylcellulose; Polyvinylpyrrolidon; Schellack; und Methacrylsäure-Copolymeren besteht.

10. Dosierungseinheitsform nach Anspruch 1, **dadurch gekennzeichnet, daß** besagtes wasserunlösliche filmbildende Polymer ausgewählt ist aus der Gruppe, die aus Cellulosederivaten; Acrylharzen; Copolymeren von Acrylsäure- und Methacrylsäureestern mit quartären Ammoniumgruppen; und Copolymeren von Acrylsäure- und Methacrylsäureestern besteht.

11. Dosierungseinheitsform nach Anspruch 1, **dadurch gekennzeichnet, daß** besagtes die Durchlässigkeit verringernde Mittel ausgewählt ist aus der Gruppe, die aus Fettsäuren; Wachsen; und den Salzen der Fettsäuren besteht.

12. Dosierungseinheitsform nach Anspruch 1, **dadurch gekennzeichnet, daß** besagtes wasserlösliche filmbildende Polymermittel ausgewählt ist aus der Gruppe, die aus Celluloseacetatphthalat; Celluloseacetattrimellitat; Hydroxypropylmethylcellulosephthalat; Hydroxypropylmethylcellulose; Polyvinylpyrrolidon; Schellack; und Methacrylsäure-Copolymeren besteht.

13. Dosierungseinheitsform nach Anspruch 1, **dadurch gekennzeichnet, daß** besagtes wasserunlösliche filmbildende Polymer nicht weniger als die Hälfte der Membran umfaßt.

14. Verfahren zur Herstellung einer Dosierungseinheitsform zur Freisetzung eines Arzneistoffes in eine wäßrige flüssige Umgebung in einer Reihe von sequentiellen, stoßweisen Freisetzungsereignissen, wobei das Verfahren die Schritte umfaßt:

A) Herstellen einer Mehrzahl von Pellets oder Teilchen, die einen Arzneistoff und ein von besagtem Arzneistoff verschiedenes Quellungsmittel umfassen;

B) vollständiges Umhüllen jedes Pellets oder Teilchens in einer wasserdurchlässigen zerbrechlichen Umhüllung oder Membran, wobei die Membran so angeordnet ist, daß sie Wasser zu besagtem Quellungsmittel zuläßt und bricht, wenn besagtes Quellungsmittel sich ausgedehnt und dadurch eine bestimmte Kraft auf besagte Membran ausgeübt hat;

C) Herstellen besagter Umhüllung aus einer Mischung, die wasserdurchlässiges unlösliches filmbildendes Polymer, wasserdurchlässiges lösliches filmbildendes Polymer und ein die Durchlässigkeit verringerndes Mittel umfaßt;

D) Unterteilen besagter Pellets in eine Mehrzahl von Populationen von Pellets, in der jede Population mit Pellets versehen ist, die eine Umhüllung aufweisen, die so angeordnet ist, daß bewirkt wird, daß besagte Pellets in einem bestimmten Aufbrechzeitintervall, nachdem sie besagter wäßrigen flüssigen Umgebung ausgesetzt worden sind, aufbrechen und den Arzneistoff freisetzen, und Versehen jeder Population mit einer Umhüllung mit einem unterschiedlichen Aufbrechzeitintervall, um dadurch besagte sequentielle, stoßweise Freisetzungsereignisse bereitzustellen;

E) Mischen der Mehrzahl von Populationen von Pellets in einer Mischung mit vorbestimmten Anteilen; und

F) vollständiges Einschließen eines Aggregats besagter Mischung in eine Kapsel oder Tablette, die in einer wäßrigen flüssigen Umgebung zerfällt und besagte Pellets im wesentlichen gleichzeitig freisetzt, um sie besagter wäßrigen flüssigen Umgebung auszusetzen, um dadurch eine Dosiseinheit herzustellen, in der besagtes wasserdurchlässige lösliche filmbildende Polymer sich allmählich auflöst und bewirkt, daß besagte Umhüllung zunehmend zerbrechlich wird, wenn die Kontaktzeit mit der wäßrigen flüssigen Umgebung zunimmt, und besagtes die Durchlässigkeit verringernde Mittel die Geschwindigkeit verringert, mit der Wasser durch die Membran hindurchgeht, und dadurch die Ausdehnung besagten Quellungsmittels, und die relativen Mengen an besagtem löslichen filmbildenden Polymer und besagtem die Durchlässigkeit verringernden Mittel in Umhüllungen jeder Population, und die Dicke der Umhüllung, besagtes bestimmte Aufbrechzeitintervall bestimmen.

15. Verfahren nach Anspruch 14, **dadurch gekennzeichnet, daß** die relativen Anteilen an unlöslichem filmbildenden Polymer, löslichem filmbildenden Polymer und die Durchlässigkeit verringerndem Mittel in den Umhüllungen aller besagten Populationen konstant gehalten werden und unterschiedliche Aufbrechzeitintervalle durch Variieren der Umhüllungsdicke erreicht werden.

16. Verfahren nach Anspruch 14, **dadurch gekennzeichnet, daß** unterschiedliche Aufbrechzeitintervalle durch Variieren der relativen Anteile an besagtem löslichen filmbildenden Polymer, besagtem unlöslichen filmbildenden Polymer und besagtem die Durchlässigkeit verringernden Mittel erreicht werden.

Revendications

1. Forme de dosage unitaire pour libérer un médicament dans un environnement contenant un fluide aqueux en un certain nombres d'événements libérateur pulsatiles séquentiels, ladite forme de dosage unitaire comprenant :

A) une capsule ou un comprimé qui se désintègre dans un environnement aqueux d'utilisation ;
B) un certain nombre de populations de boulettes ou particules enfermées dans ladite capsule ou ledit comprimé, chaque population de boulettes construite pour libérer un médicament dans ledit environnement d'utilisation en éclatant à un intervalle de temps de libération particulier différent après contact initial avec ledit environnement d'utilisation, toutes lesdites boulettes étant ainsi libérées par ladite capsule ou ledit comprimé sensiblement simultanément et exposées audit environnement d'utilisation sensiblement simultanément quand ladite capsule ou ledit comprimé se désintègre ;

C) chaque boulette contenant un noyau comprenant ledit médicament et un agent gonflant autre que ledit. médicament, ledit agent gonflant ayant la propriété d'augmenter en volume lors d'une exposition à l'eau ;
D) une membrane frangible, perméable à l'eau, renfermant complètement ledit noyau et empêchant la libération dudit médicament dans ledit environnement d'utilisation, ladite membrane comprenant au moins un polymère formant un film insoluble dans l'eau et au moins l'un de :

a) un moyen formant polymère formant un film soluble dans l'eau qui se dissout graduellement et force ladite membrane à devenir de plus en plus frangible tandis que le temps en contact avec l'eau augmente ; et

b) un moyen réduisant la perméabilité qui réduit le taux auquel l'eau passe à travers la membrane et ainsi le le taux d'augmentation de volume de l'agent gonflant dans le noyau, ainsi l'augmentation de volume dudit agent gonflant applique une force interne croissante sur ladite membrane et le taux auquel ladite force est appliquée est déterminé par la perméabilité à l'eau de ladite membrane et la force interne à laquelle ladite membrane éclatera est déterminée par la frangibilité de ladite membrane et le médicament est libéré vers ledit environnement d'utilisation quand la membrane renfermant ledit noyau éclate.

2. Forme de dosage unitaire selon la revendication 1, dans laquelle toutes les populations ont des membranes avec la même composition et le temps particulier de libération d'une population est déterminé par l'épaisseur de ladite membrane.

3. Forme de dosage unitaire selon la revendication 1, dans laquelle le temps particulier de libération d'une population est déterminé au moins partiellement par les proportions relatives dudit polymère formant un film insoluble, dudit moyen formant polymère formant un film soluble dans l'eau et dudit moyen réduisant la perméabilité dans ladite membrane.

4. Forme de dosage unitaire selon la revendication 1, dans laquelle ledit moyen formant polymère formant un film soluble dans l'eau a une plus grande solubilité au pH alcalin.

5. Forme de dosage unitaire selon la revendication 1, dans laquelle ledit moyen formant un polymère formant un film soluble dans l'eau est sensiblement soluble aux pH alcalin, neutre et acide.

6. Forme de dosage unitaire selon la revendication 1, dans laquelle ledit agent gonflant est sélectionné dans le groupe consistant en : polyvinyle pyrrolidone réticulée ; carboxyméthulcellulose réticulée ; glycolate de sodium amidon et amidon prégélatinisé.

7. Forme de dosage unitaire selon la revendication 6, dans laquelle ledit polymère formant un film insoluble dans l'eau est sélectionné dans le groupe consistant en dérivés de cellulose ; résines acryliques ; copolymères d'esters d'acide acrylique et d'acide méthacrylique avec des groupes ammonium quaternaire ; et copolymères d'esters d'acide acrylique et d'acide méthacrylique.

8. Forme de dosage unitaire selon la revendication 7, dans laquelle ledit moyen réduisant la perméabilité est sélectionné dans le groupe consistant en acides gras ; cires et les sels des acides gras.

9. Forme de dosage unitaire selon la revendication 8, dans laquelle ledit moyen formant un polymère formant un film soluble dans l'eau est sélectionné dans le groupe consistant en : acétate phtalate de cellulose ; acétate trimellitate de cellulose ; phtalate d'hydroxypropyl méthylcellulose ; hydroxypropyl méthylcellulose ; polyvinyl pyrrolidone ; shellac ; et copolymères d'acide méthacrylique.

10. Forme de dosage unitaire selon la revendication 1, dans laquelle ledit polymère formant un film insoluble dans l'eau est sélectionné dans le groupe consistant en : dérivés de cellulose ; résines acryliques ; copolymères d'esters d'acide acrylique et d'acide méthacrylique avec des groupes ammonium quaternaire ; et copolymères d'esters d'acide acrylique et d'acide méthacrylique.

11. Forme de dosage unitaire selon la revendication 1 dans laquelle ledit moyen réduisant la perméabilité est sélectionné dans le groupe consistant en : acides gras ; cires et les sels des acides gras.

12. Forme de dosage unitaire selon la revendication 1, dans laquelle ledit moyen formant polymère formant un film soluble dans l'eau est sélectionné dans le groupe consistant en : acétate phtalate de cellulose ; acétate trimellitate

de cellulose ; phtalate d'hydroxypropyl méthylcellulose ; hydroxypropyl méthylcellulose ; polyvinyl pyrrolidone ; shellac et copolymères d'acide méthacrylique.

13. Forme de dosage unitaire selon la revendication 1, dans laquelle ledit polymère formant un film insoluble dans l'eau ne forme pas moins de la moitié de la membrane.

14. Méthode de préparation d'une forme de dosage unitaire pour libérer un médicament dans un environnement d'un fluide aqueux dans une série d'événements libérateurs pulsatiles, séquentiels, la méthode comprenant les étapes de :

A) préparer un certain nombre de boulettes ou particules comprenant un médicament et un agent gonflant autre que ledit médicament ;
B) enfermer complètement chaque boulette ou particule dans un revêtement ou membrane frangible perméable à l'eau, la membrane étant agencée pour admettre de l'eau vers ledit agent gonflant et pour éclater quand ledit agent gonflant s'est dilaté et ainsi a appliqué une force particulière sur ladite membrane ;
C) composer ledit revêtement à partir d'un mélange comprenant : un polymère formant un film insoluble perméable à l'eau, un polymère formant un film soluble perméable à l'eau ; et un agent réduisant la perméabilité ;
D) diviser lesdites boulettes en un certain nombre de populations de boulettes où chaque population est pourvue de boulettes ayant un revêtement agencé pour forcer lesdites boulettes à éclater et à libérer le médicament à un intervalle particulier de temps d'éclatement après avoir été exposées audit environnement de fluide aqueux et donner à chaque population un revêtement ayant un intervalle de temps d'éclatement différent pour ainsi produire lesdits événements libérateurs pulsatiles séquentiels ;
E) mélanger les populations de boulettes dans un mélange à une proportion prédéterminée ; et
F) enfermer complètement un agrégat dudit mélange dans une capsule ou un comprimé qui se désintègre dans un environnement d'un fluide aqueux et libère lesdites boulettes pour exposition audit environnement de fluide aqueux sensiblement simultanément, pour ainsi préparer une dose unitaire dans laquelle ledit polymère formant un film soluble perméable à l'eau se dissout graduellement et force ledit revêtement à devenir de plus en plus frangible tandis que le temps en contact avec l'environnement du fluide aqueux augmente et ledit agent réduisant la perméabilité diminue le taux auquel l'eau passe à travers la membrane et ainsi la dilatation dudit agent de gonflement et les quantités relatives dudit polymère formant un film soluble et dudit agent réduisant la perméabilité dans des revêtements de chaque population et l'épaisseur du revêtement déterminent ledit intervalle de temps d'éclatement particulier.

15. Méthode selon la revendication 14, dans laquelle les proportions relatives du polymère formant un film insoluble, du polymère formant un film soluble et de l'agent réduisant la perméabilité sont maintenues constantes dans les revêtements de toutes lesdites populations et différents intervalles de temps d'éclatement sont obtenus en changeant l'épaisseur du revêtement.

16. Méthode selon la revendication 14, dans laquelle différents intervalles de temps d'éclatement sont agencés en variant les proportions relatives dudit polymère formant un film soluble, dudit polymère formant un film insoluble et dudit agent réduisant la perméabilité.

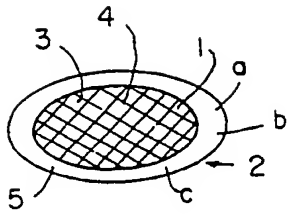


FIG. 1

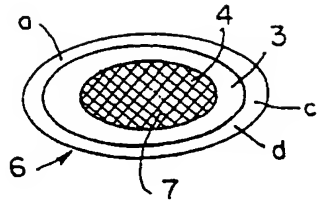


FIG. 2

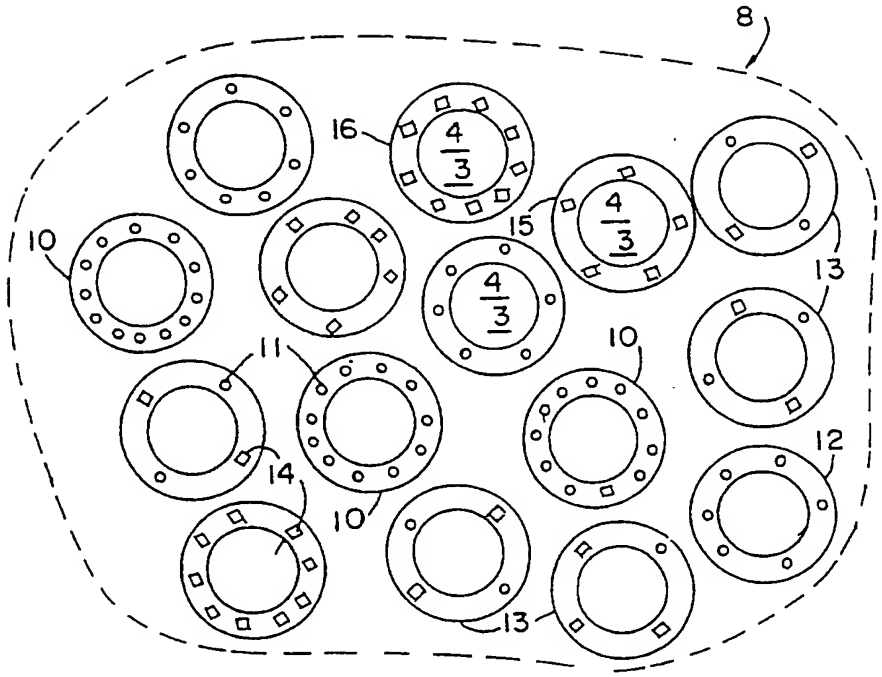
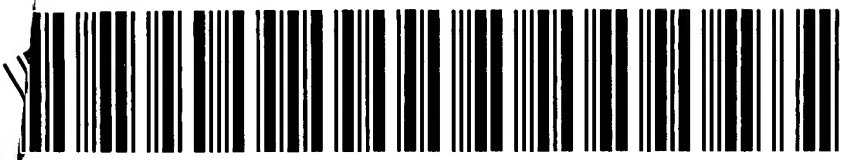


FIG. 3

IDS REFERENCES



☐ FOR

EXAMINATION REPORT

☒ 1st Examination Report ☐ 2nd Examination Report

Application No.	Application Filing Date (day/Month/year)	Priority Date (day/Month/year)
05 26 0068	26/03/2005	26/03/2004

Applicant:

Eisai R&D Management Co., Ltd.

Local Agent:

Suleiman Ibrahim Al-Ammar

1. ☐ The Report is accompanied by a copy of each cited prior art document.

2. ☐ Certain claims were found unpatentable (for specific reason) (See Box I).

3. ☐ Unity of invention is lacking (See Box II).

4. ☒ Certain claims were found unpatentable (**novelty, inventive step or industrial applicability**) (See Box III).

5. **Title of Invention:**

☒ The text is approved as submitted by the applicant.

☐ The text is rejected and the Patent Office suggests the title to read as follows:

6. The figure of the drawings to be published with the abstract is:

Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterises the invention.

☒ None of the figures.

	Application No. 05 26 0068

A. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC)
Int Cl

B. The Patent Office is reporting only on the main invention of claims

☒ All Claims ☐ Claims

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	US 5035899	Claims 1-30
X	Free Sale Certificate of Pariet™ tablet which was presented to the Saudi Ministry of Health on 16/07/1998.	Claims 1-30
X	As per the Orange Book, issued by the American Food and Drugs Administration, the same composition (Acifex) has been in use since 19/8/1998.	Claims 1-30
X	EP 06 70 718	Claims 1-30

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

A	document defining the general state of the art which is not considered to be of particular relevance	T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
E	earlier document but published on or after the international filing date	X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation	Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
O	other special reason or other means (as specified)	&	document member of the same patent family
P	document published prior to the international filing date but later than the priority date claimed		

	Application No. 05 26 0068

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	Aciphex information sheet , issued by the manufacturing company on August 2003.	Claims 1-30
X	Japan Corporate News Network, dated 8/07/2004 and 16/03/2005.	Claims 1-30
X	PipelineReview.com magazine dated 22 July 2007.	Claims 1-30

	Application No. 05 26 0068

Box I Observation where certain claims were found unsearchable (continuation of item 2 of first sheet)

This/ These certain claims has/have been rejected for the following reason:

☐ Claims Nos.

Because they do not meet the patentabilty requirements by the Saudi Patent Law, namely,

☐ This / These claim(s) relate(s) to discoveries, scientific theories and mathematical methods which is/ are not patentable in accordance with Article 45/a of the Saudi Patent Law.

☐ This / These claim(s) relate(s) to schemes, rules and methods of conducting commercial activities, exercising pure mental activities, Computer Software or playing a game which is/ are not patentable in accordance with Article 45/b of the Saudi Patent Law.

☐ This / These claim(s) relate(s) to the treatment of human being which is/ are not patentable in accordance with Article 45/d of the Saudi Patent Law.

The applicant has the following available options:

- Deleting the rejected claim(s).
- Converting the claim(s) into the Swiss-type format (e.g., Use of compound X in the manufacture of a medicament for the treatment of indication Y.)

☐ This / or These claim(s) is/ are not clear enough & do(es) not give a full definition of the required scope of protection

Box II Observation where unity of invention is lacking (continuation of item 3 of first sheet)

This office found multiple inventions in this application, as follows:

	Application No. 05 26 0068

Box III Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	YES
	Claims 1-30	NO
Inventive step (IS)	Claims	YES
	Claims 1-30	NO
Industrial applicability (IA)	Claims 1-30	YES
	Claims	NO

2. CITATIONS AND EXPLANATIONS

This office found multiple inventions in this application, as follows:

NOVELTY (N) Claims

INVENTIVE STEP (IS) claims